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FLEX study: Prognostic factors in NSCLC

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Background: The phase III FLEX study demonstrated that addition of cetuximab to a standard 1st-line platinum-based chemotherapy (cisplatin/vinorelbine) significantly improves survival, compared with chemotherapy alone, in patients with advanced EGFR-expressing NSCLC.
Materials and Methods: Patients were randomized to receive chemotherapy plus cetuximab (n = 557) or chemotherapy alone (n = 568). Both univariate and multivariate analyses were used to identify factors with prognostic significance, independent of cetuximab treatment.
Results: Baseline characteristics of the ITT population (n = 1125) were as follows: median age 59 years (range 18−83 years), 31% aged >65 years, 70% male, 83% ECOG performance status 0/1, 94% stage IV disease, 47% adenocarcinoma, and 34% squamous cell carcinoma. Prognostic factors identified by univariate analysis were ethnicity, smoking status, histologic subtype, performance status, and gender. Median survival time was longer for Asian patients (n = 121; 19.5 months) than Caucasian patients (n = 946; 9.6 months). Never-smokers, former smokers, and smokers had respective median survival times of 14.6, 11.1, and 9.0 months. Median survival time was 12.4 months for patients with adenocarcinomas, compared with 9.3 months for those with squamous cell carcinomas. ECOG performance status of 0, 1, or 2 was associated with corresponding median survival times of 13.5, 10.6, or 5.9 months. Females had longer median survival times than males (12.7 vs 9.3 months, respectively). Age (<65 or $\geqslant$65 years) was not identified as a prognostic factor. Prognostic significance of the following factors was verified by multivariate analysis: region (Europe vs Australasia), smoking status, histologic subtype, and gender.
Conclusions: Findings from the FLEX study in advanced NSCLC confirmed the prognostic value of ethnicity, smoking status, histologic subtype, performance status, and gender, independent of cetuximab treatment.

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EGFR, KRAS, PIK3CA mutations and response to tyrosine kinase inhibitors (TKIs) in advanced NSCLC patients

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Background: Molecular alterations of the *EGFR* pathway are considered the major determinant of clinical outcome in response to EGFR TKIs in non small cell lung cancer (NSCLC) patients (pts). The aim of this study was to determine the clinical implication of *EGFR, KRAS, PIK3CA* gene mutations in pts with advanced NSCLC who had been treated with gefitinib or erlotinib after failure of 1st or 2nd-line platinum-based chemotherapy.
Methods: Genomic DNA was isolated from paraffin-embedded tumor specimens, amplified for *EGFR* (exons 18, 19, 20 and 21), *PIK3CA* (exons 9 and 20) *KRAS* (exon 2) by nested polymerase chain reaction and sequenced in both sense and antisense directions. RECIST criteria were used to assess response to TKIs.
Results: One hundred twenty-eight pts have been treated with TKIs. Median age was 60 yrs (range 25−81.5), M/F: 71/57, ECOG-PS 0/1/2/3: 82/39/6/1; stage IIIB/IV: 36/92; adeno/bac/squamous/large-cells/other: 82/10/25/3/8; never/former/current smokers:43/28/46. *EGFR* mutations were detected in 31 of 122 pts (25%); 20 (16.4%) had deletional mutations in exon 19, 6 (4.7%) had point mutations in exon 20 and 6 (4.7%) in exon 21. One pt had two mutations (exon 19: delE746-A750, exon 20: missense mutation T790M). *KRAS* and *PIK3CA* mutations were detected in 5.7% and in 2.7% of pts, respectively. Overall, pts with *EGFR* mutations had a response rate (RR) of 50.0% vs 19.8% (p = 0.001), disease control rate of 66.2% vs 49.4% (p = 0.02) median time to progression of 7 months vs 3 months (p = 0.06) with respect to *EGFR* non mutated pts. No difference in overall median survival was observed. However when we considered 25 pts with TKI-sensitive *EGFR* mutations (deletion in exon 19, missense L858R) we observed a significant longer TTP (p = 0.008, median 8 vs 3 months in non mutants) and a better OS (p = 0.07, median not reached vs 11 months in *EGFR* non mutants). In this setting the RR was 88% (22 of 25) and TTP was significantly better also in the multivariate analysis (p = 0.01). All pts with *KRAS* mutations did not responded to TKIs treatment as the pts with *PIK3CA* mutations.
Conclusions: In this experience we confirmed that *EGFR* mutations (deletion in exon 19, missense L858R) are the most important predictor of TKI sensitivity. In addition the evaluation of *KRAS* and *PIK3CA* mutations could contribute to identify lung cancer patients who are most suitable for TKIs treatment.

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Phase I dose-escalation study of vorinostat in combination with gemcitabine and cisplatinum in patients with advanced non-small-cell lung cancer (NSCLC)

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Background: Preclinical data suggest that the histone deacetylase inhibitor vorinostat (Zolinza®) enhances the efficacy of gemcitabine and platinum chemotherapy agents. This study investigated the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of vorinostat combined with gemcitabine and a platinum agent in patients (pts) with advanced NSCLC.
Material and Methods: Eligible pts (aged $\geqslant$18 years; Stage IIIB/IV NSCLC, ECOG performance status $\leqslant$1, no prior systemic chemotherapy [except adjuvant]) were sequentially enrolled on escalating doses of vorinostat plus gemcitabine and a platinum agent (standard 3+3 design) for $\leqslant$6 cycles (Table). Carboplatin regimens were to be investigated if dose levels (DLs) 1 or 2 exceeded the MTD.
Results: 38 pts enrolled to date (M/F: 29/9; median age: [range] 55.5 [32−70] years) at 5 DLs (Table). Two pts had DLTs: elevated creatinine leading to cisplatin dose reduction (DL 2) and febrile neutropenia (DL 5) (Table). 14 additional pts have been enrolled in an expansion cohort and will be treated at DL 4. 85% of adverse events (AEs) were mild/moderate and 32 pts (84%) had Grade 3 AEs. The most common drug-related Grade 3/4 AEs were neutropenia (14 pts), thrombocytopenia (10 pts) and asthenia (10 pts). Serious AEs occurred in 23 pts and there were 7 deaths (1 'probably', 1 'possibly' and 5 'definitely not' treatment-related). Of 31 pts with CT assessments available (as of April 2009), 11 (35%) had partial response, 15 (48%) had stable disease, and 5 (16%) had progressive disease (Table). Updated results will be presented.
Conclusions: These Phase I data suggest that vorinostat combined with standard doses of gemcitabine and cisplatin is active in the initial treatment of metastatic NSCLC: randomised trials are needed to determine whether addition of vorinostat improves outcomes in such pts.

Cohort	No. of patients enrolled	Vorinostat (mg/day) Start day 1	Gemcitabine (mg/m^2) Days 3 & 10	Cisplatin (mg/m^2) Day 3	DLTs	Responses
1	4	300 × 7	1000	75		1 PR, 1 SD, 1 PD, 1 NE
2	6	300 × 7	1250	75	Cisplatin dose reduction[a]	3 PR, 2 SD, 1 PD
3	4	400 × 7	1250	75		3 SD, 1 NE
4	3	400 × 10	1250	75		2 PR, 1 SD
DL 4 Expansion	14	400 × 10	1250	75		1 PR, 7 SD, 3 PD, 3 NE
5	7	400 × 14	1250	75	Febrile neutropenia[b]	4 PR, 1 SD, 2 NE

NE, not yet evaluable; PR, partial response; SD, stable disease; PD, progressive disease; DL, dose level. [a]Due to elevated creatinine levels (any drug-related AE leading to a dose reduction was defined as a DLT); [b]Another patient enrolled at DL 5 discontinued